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POSTTRAUMATIC STRESS DISORDER, ALLOSTATIC LOAD, AND MEDICAL ILLNESS

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In this chapter we present a psychobiological conceptual framework that accounts for the mounting evidence that posttraumatic stress disorder (PTSD) is a risk factor for medical illness. First we describe the human response to stress to provide the context for the ensuing discussion. Then we summarize the extensive literature on the relationship of chronic stress syndrome to medical illness. Next we review the biological alterations associated with chronic PTSD and how these PTSD-related psychobiological abnormalities might increase the risk for medical illness among affected individuals. Then we introduce the allostatic load model (McEwen, 1998; McEwen & Stellar, 1993) and demonstrate how this theoretical approach enables us to understand the etiological significance of such abnormalities. Finally, we discuss how the allostatic load model helps us conceptualize resilience, prevention, and treatment.

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BACKGROUND AND CONCEPTUALIZATION

In 1995, Friedman and Schnurr (1995) observed that exposure to trauma was associated with poor health outcomes and proposed that this relationship was mediated by PTSD. They suggested that biological and psychological abnormalities associated with PTSD might increase the risk for medical illness among people experiencing this disorder. At the time of that review, there were limited data for evaluating this hypothesis. Four years later, Schnurr and Jankowski (1999) reported that recent empirical findings did indeed support an association between PTSD and poor health on the basis of self-reports, clinical utilization, and medical morbidity. After considering the various biological and behavioral factors that might promote such a relationship, they suggested that the McEwen and Stellar (1993; McEwen, 1998) model of allostasis and allostatic load appeared to provide a plausible mechanism through which stress in general, and PTSD in particular, might lead to medical illness. This chapter focuses on the elaboration and application of this model to trauma, PTSD, and health.

Allostasis, as originally proposed and elaborated (McEwen, 1998; McEwen & Stellar, 1993; Sterling & Eyer, 1988) is an organizing principle for understanding the biological basis of an organism's ability to achieve stability through change—that is, of maintaining homeostasis by expending and directing energy toward challenges. Allostasis, referring to the process of adaptation, incorporates the notion of stress but also includes the contributions of genetic factors, early life experiences, and features of lifestyle that determine the nature of the physiological responses to daily life events as well as to the situations that qualify as stressors.

Allostatic load is the cumulative cost to the organism of going through repeated cycles of allostasis or adaptation. This cost may accumulate from having to respond to repeated challenges or from misdirection of the physiological responses that constitute allostasis: for example, failure to shut off production of mediators like cortisol and catecholamines, or failure to habituate to repeated challenges of the same kind. Mismanagement also includes the failure to mount an adequate response to a challenge: for example, inadequate glucocorticoids leading to overproduction of inflammatory cytokines. Allostatic load may result from the sustained activity of mediators of allostasis, referred to as an *allostatic state*: for example, elevated blood pressure in hypertension, elevated inflammatory cytokine production when glucocorticoid levels are inadequate, or elevated diurnal production of glucocorticoids in major depressive illness that contribute to bone mineral loss, abdominal obesity and atrophy of brain structures (see McEwen, 1998). In other words, sustained allostatic load can lead to medical illness.

From the perspective of allostatic load, PTSD is extremely complex. This is because humans who fail to meet the demands of traumatic stressors

use and perturb many key psychobiological mechanisms that have evolved for coping, adaptation, and preservation of the species (Friedman, 1999; Friedman, Charney, & Deutch, 1995). Thus, we propose that allostatic load is a rich heuristic model through which to understand the many complex psychobiological abnormalities associated with PTSD. As we attempt to demonstrate, it is also a useful context for understanding why these abnormalities make PTSD a risk factor for medical illness. We conclude that allostatic load provides a new framework for understanding PTSD and its comorbidities. We also propose a new term, *allostatic support*, to refer to mechanisms that confer resilience on individuals, making them more resistant to PTSD and other chronic illnesses.

THE HUMAN RESPONSE TO STRESS

The human stress system has evolved to maintain allostasis, especially in response to significant challenges that might be characterized as stressors. It consists of the central and peripheral nervous systems, the endocrine system, and the immunological system. The two major components of the stress system are the hypothalamic–pituitary–adrenocortical (HPA) axis and the locus coeruleus/norepinephrine-sympathetic system (LC/NE system).

Corticotropin releasing factor (CRF) might be considered the ignition switch for the human stress response because it has a key role in activating both HPA and LC/NE systems. In the HPA axis, CRF is secreted from the hypothalamus, after which it releases adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH then promotes the release of cortisol and other glucocorticoids from the cortex of the adrenal gland. Maintenance of the integrity of the HPA system is crucial for normal coping and adaptation (Selye, 1956). As discussed subsequently, this integrity is not maintained in PTSD. Indeed, a large body of evidence indicates that HPA abnormalities figure prominently in the pathophysiology of PTSD.

The second major system, the LC/NE system, includes adrenergic mechanisms in both the central nervous system (CNS) and the peripheral sympathetic nervous system (SNS). The LC/NE component of the stress response was first described by Cannon (1932) as the classic "fight-or-flight response." The two neurotransmitters in the adrenergic system, norepinephrine and epinephrine, are collectively called catecholamines because of their similar chemical structure. CRF also has a major role in the LC/NE system in which it functions as the principal neurotransmitter that activates the locus coeruleus, a midbrain structure that contains the majority of the brain's adrenergic neurons (Aston-Jones, Valentino, Van Bockstaele, & Meyerson, 1994). There is abundant evidence that the LC/NE system also functions abnormally in PTSD.

BIOLOGICAL ABNORMALITIES ASSOCIATED WITH CHRONIC STRESS

The human stress response evolved as an acute reaction for coping with a significant challenge or threat. The effectiveness of such a reaction is measured not only by the efficiency with which it mobilizes physiological, neurohormonal, and immunological mechanisms, but also by how quickly organismic function can return to prestress homeostatic and allostatic levels. Indeed, recovery of the baseline steady state is as important a part of coping, adaptation, and resilience as is the capacity to mount an effective stress response in the first place (Dienstbier, 1989; McEwen, 1998).

Sometimes recovery does not occur or cannot be achieved. This may happen because the stressor itself continues to persist for a protracted period of time. At other times, return to homeostasis or allostasis is impossible because the organism lacks the capacity to implement those mechanisms needed for recovery. Under such circumstances, psychobiological alterations designed for a time-limited reaction persist as chronic stress syndrome, which we shall consider from the perspective of allostatic load. For now, we focus on specific alterations in biological function.

Chronic stress syndrome (Chrousos, 1998; McEwen, 1998) is associated with sustained abnormalities in key biological systems. Persistent elevation in CRF secretion promotes increased HPA, SNS, LC/NE, and opioid function. Table 7.1 (Column 2) shows that activation of HPA function is associated with higher ACTH and cortisol and reduced dehydroepiandrosterone (DHEA) levels. Physiological and LC/NE enhancement is associated with increased SNS and adrenergic reactivity as well as elevations in tonic (steady state) function. Endogenous opioid mechanisms are also enhanced during chronic stress. A major consequence of CRF-induced increased activity in these systems is a reduction of activity in others. As shown in Table 7.1, reproductive, growth, and immunological mechanisms in particular exhibit significant deficits in function as part of chronic stress syndrome. Readers seeking more information are referred to comprehensive reviews on this subject by Chrousos (1998) and McEwen (1998).

MEDICAL ABNORMALITIES ASSOCIATED WITH CHRONIC STRESS SYNDROME

Biological abnormalities that comprise chronic stress syndrome may have adverse health consequences leading to medical illness. More detailed review of this important and complex topic may be found elsewhere (Chrousos, 1998; McEwen, 1998). Table 7.2 (Column 2) summarizes some of the most prominent medical problems addressed in those comprehensive

TABLE 7.1
Biological Abnormalities Associated With Chronic Stress Syndrome and PTSD

System	Chronic stress syndrome	PTSD
HPA	Increased HPA activity ↑CRF, ↑Cortisol, ↓DHEA ?↓GR sensitivity	HPA dysregulation ↑CRF ?↓/↑Cortisol ?↑GR sensitivity
Physiological (SNS)	↑SNS reactivity ↑Tonic SNS activity Disrupted sleep	↑SNS reactivity, ↑Tonic SNS arousal ↑Startle response Disrupted sleep
LC/NE (Adrenergic)	↑Adrenergic reactivity ↑Catecholamine levels	↑Adrenergic reactivity ↑Tonic adrenergic activity Downregulation α_2/β receptors Blunted NPY activity
Opioids	↑Endogenous opioids (↑β endorphin)	↓/↑Endogenous opioids (tonic dysregulation) Phasic hyperactivity
Thyroid	↓TSH, ↓T3 ↓T3/T4 ratio	↑T3, ↑T4 ↑T3/T4 ratio
Reproductive	↓GnRH men: ↓LH, ↓testosterone women: ↓LH, ↓FSH, estradiol	?↓/↑testosterone
Growth	↓GH ↓Growth factors (IGF-1)	Normal GH levels ↓GH activation by clonidine or levodopa (in abused boys)
Metabolic	Metabolic syndrome X (see Table 7.2)	Osteopenia
Immunologic	Immunosuppression ↑Inflammatory cytokines (IL-1, IL-2, IL-6, TNFs)	Immunosuppression ↑Inflammatory cytokines

Note. HPA = hypothalamic–pituitary–adrenocortical; CRF = corticotropin releasing factor; DHEA = dehydroepiandrosterone; GR = glucocorticoid receptor; SNS = sympathetic nervous system; TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; GnRH = gonadotropin releasing hormone; LH = lutelnizing hormone; FSH = follicle stimulating hormone; GH = growth hormone; IGH = insulin-like growth factor; IL = interleukin; TNF = tissue necrosis factor.

reviews. It can be seen that SNS and LC/NE system dysregulation may result in a variety of cardiovascular changes that are clinically significant including atherosclerosis, hypertension, cardiac arrhythmias, compromised coronary function, and increased risk for myocardial infarction and stroke. Immunological consequences range from impaired immunological capacity (e.g., immunosuppression) to episodic inflammatory and autoimmune disorders. Hormonal suppression may affect all aspects of reproductive function as well as normal growth and development. Metabolic syndrome X is a

TABLE 7.2
Medical Problems Associated With Chronic Stress Syndrome and PTSD

System	Chronic stress syndrome	PTSD
HPA	Hypercortisolism and Cushing's Disease, as well as endocrine, reproductive, metabolic, and immunological problems (shown below)	?Hypo- or Hypercortisolism, as well as endocrine, reproductive, metabolic, and immunological problems (shown below)
SNS/LC/NE	*Cardiovascular abnormalities* Atherosclerosis Hypertension Cardiac arrhythmias EKG abnormalities Damaged myocardium Myocardial infarction Stroke Increased coronary vascular tone Increased coronary turbulence and shearing forces Increased platelet aggregation	*Cardiovascular abnormalities* Angina ↓ Effort tolerance Peripheral vascular illness EKG abnormalities
Opioids	*Chronic* Hyperalgesia Pain syndromes Headaches	*Chronic pain syndromes* Hyperalgesia
Thyroid	Hyperthyroidism	?Hyperthyroidism
Reproductive	*Reproductive abnormalities* Infertility, spontaneous abortion, ectopic pregnancy, preterm contractions, excessive fetal growth Possible *Congenital abnormalities* Conotruncal heart defects Neural tube defects Cleft lip with or without cleft palate	Reproductive abnormalities (one study)
Growth	Possible interference with normal growth and development (especially during critical periods)	No research
Metabolic	*Metabolic Syndrome X* Dyslipidemia, visceral adiposity, insulin resistance, Type II diabetes, hypertension, excessive clotting or deficient fibrinolysis Osteopenia and osteoporosis	Osteopenia (one study) No other research
Immunological	*Immunosuppression* Increased disease susceptibility Delayed wound healing Retarded immunization response Suppressed delayed-type hypersensitivity	*Immunosuppression* ↑ Disease susceptibility (one study)

(continued)

TABLE 7.2 *(Continued)*

System	Chronic Stress Syndrome	PTSD
	Inflammatory and autoimmune disorders Irritable bowel syndrome Rheumatoid arthritis Type I diabetes Chronic fatigue syndrome Fibromyalgia Temperomandibular disorders Tension headaches Dysmenorrhea Irritable bladder syndrome Multiple chemical sensitivity	*Inflammatory and autoimmune disorders* Stress-induced exacerbation of chronic fatigue syndrome (one study)

complex cluster of symptoms resulting from HPA suppression of growth hormone, gonadal steroids, and bone production; the clinical manifestations are Type II diabetes, visceral adiposity, and atherosclerosis (from insulin resistance and carbohydrate intolerance, abnormal lipid metabolism, and excessive blood clotting or deficient fibrinolysis). Osteoporosis is another manifestation of metabolic syndrome X that affects women more than men (because suppression of estrogen impairs bone growth).

In the following sections, we consider biological abnormalities and medical problems associated with PTSD. We compare PTSD-related biological abnormalities with those previously discussed with regard to chronic stress syndrome. In addition, we consider empirical observations concerning medical problems associated with PTSD and see how they compare with medical consequences due to chronic stress syndrome. It should be noted that other chapters in this book provide thorough reviews of the published literature on PTSD and health status (Green & Kimerling, chap. 2), cardiovascular illness (Ford, chap. 4), and immune function (Dougall & Baum, chap. 6).

BIOLOGICAL ABNORMALITIES ASSOCIATED WITH PTSD

As shown in Table 7.1 (Column 3), there are a number of biological abnormalities that have been detected among people with PTSD that are reviewed more extensively elsewhere (Friedman, 1999; Friedman, Charney, & Deutch, 1995; Yehuda & McFarlane, 1997). These include hyperreactivity in several physiological systems, an excessive startle reflex, and disrupted sleep. Major psychobiological systems that mediate the human response to stress are also dysregulated. Empirical research has detected significant alterations in neurotransmitter and neuroendocrine activity involving the

HPA system, adrenergic mechanisms, neuropeptide Y (NPY), endogenous opioids, the hypothalamic–pituitary–thyroid (HPT) axis, the hypothalmic–pituitary–gonadotropic (HPG) axis, and the immune system (with respect to both humoral and cell-mediated mechanisms). In many respects, PTSD-related abnormalities are similar to those found in chronic stress syndrome. But there are intriguing differences and there are many gaps in our knowledge.

Hypothalamic–Pituitary–Adrenocortical System

A large body of evidence indicates that HPA abnormalities figure prominently in the pathophysiology of PTSD. Investigations have focused mostly on CRF release, cortisol levels, and glucocorticoid receptor sensitivity. There also appear to be important gender-related differences in HPA function.

Corticotropin Releasing Factor

As stated previously, CRF is the ignition switch for the cascade of reactions that constitute the human stress response. It initiates both the HPA and LC/NE systems as well as other neurotransmitter, neurohormonal, metabolic, and immunological responses. Studies with male combat veterans and premenopausal survivors of childhood sexual abuse have detected elevated cerebrospinal fluid, CRF levels, and enhanced hypothalamic release of CRF, among people with PTSD compared to those without PTSD (Baker et al., 1999; Bremner, Licinio, et al., 1997; Yehuda et al., 1996). Mixed results have been found with respect to the ACTH response to CRF (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Smith et al., 1989). This suggests that CRF function is dysregulated in people with PTSD.

Cortisol Levels

Findings on urinary free cortisol levels are mixed. Earlier studies with male combat veterans and elderly male and female Holocaust survivors generally found reduced 24-hour urinary cortisol levels in those with PTSD compared to trauma survivors without PTSD. Other studies with male veterans have shown no difference. More recent investigations, mostly with premenopausal women and traumatized children, have found the opposite (i.e., elevated urinary cortisol levels) among those with PTSD (see reviews by Heim, Ehlert, & Hellhammer, 2000; Rasmusson & Friedman, 2002; Rasmusson et al., 2001; Yehuda, 1999).

It is not clear how to explain such variable findings. Some investigators have cited methodological differences (Rasmusson et al., 2001; Yehuda,

1999). Rasmusson has also suggested that gender differences may account for some of this variability (see Rasmusson & Friedman, 2002).

Finally, the question of tonic versus phasic HPA abnormalities in PTSD must be considered carefully. Mason, Giller, Kosten, and Wahby (1990) measured urinary cortisol levels in hospitalized combat veterans with PTSD at admission, midpoint, and discharge. Remarkable fluctuations were seen throughout the hospitalization. Many veterans with low urinary cortisol at admission exhibited high levels several weeks later during that phase of the hospitalization that included therapeutic reexposure of patients to stressful traumatic memories of the Vietnam War. After more weeks had passed, these same veterans reexhibited low urinary cortisol prior to discharge. The investigators proposed that baseline HPA function can fluctuate dramatically in response to external (stressful) circumstances and, therefore, that it must be monitored longitudinally if we ever hope to understand its complex expression in PTSD.

Glucocorticoid Receptor Sensitivity

HPA allostasis is maintained by a negative feedback system. CRF produces ACTH secretion, which promotes cortisol release from the adrenal cortex. The hypothalamus monitors the amount of circulating cortisol through its glucocorticoid receptors. If a sufficient number of these receptors are occupied by cortisol, CRF secretion is inhibited. This negative feedback mechanism prevents blood cortisol levels from getting too high. If cortisol levels are too low, however, and an insufficient number of hypothalamic glucocorticoid receptors are occupied, CRF is released until the proper blood cortisol level is achieved.

An important theory concerning HPA function in PTSD, derived mostly from Yehuda's work (see Yehuda, 1997, 1999), is that there is an allostatic equilibrium marked by low cortisol, an increase in the number (e.g., up-regulation) of glucocorticoid receptors, and enhanced negative feedback of the HPA system due to supersensitivity of these same glucocorticoid receptors. The paradox of this elegant model is that despite lower cortisol levels, the system may act as if there were excessive HPA activity because of the supersensitivity of the glucocorticoid receptors. Indeed, many of the research findings presented below are consistent with the hypothesis that HPA activity is elevated, not reduced, in PTSD.

To summarize, HPA function appears to be dysregulated in PTSD, although variable experimental findings make it impossible to specify a unitary pattern of abnormalities at this time. Many findings suggest enhanced HPA activity due to some combination of elevated CRF activity, glucocorticoid receptor sensitivity, and, in some cases, elevated cortisol levels. Reports vary regarding whether hypocortisolism in PTSD (and other stress-related

disorders) is or is not associated with glucocorticoid receptor supersensitivity. Such variability may reflect tonic (e.g., baseline) as well as phasic (e.g., stress-induced episodic) HPA abnormalities, the magnitude of an individual's stress response at the time of measurement, methodological issues regarding the collection and assay of urinary samples, or gender-related differences in neurohormonal factors affecting CRF, cortisol levels, or glucocorticoid receptor sensitivity.

Physiological Abnormalities in PTSD

Sympathetic Nervous System (SNS) Hyperreactivity

The other major mediator of the stress response is the sympathetic nervous system. One of the oldest and most robust findings in all PTSD research is the excessive SNS reactivity of people with PTSD to stimuli related to the traumatic event. Such stimuli may be auditory (Blanchard, Kolb, Prins, Gates, & McCoy, 1991), pictorial (Keane et al., 1998), or narrative descriptions of the traumatic experience (Pitman, Orr, Forgue, de Jong, & Clairborn, 1987). Participants with PTSD are distinguishable from trauma exposed non-PTSD comparison participants by a markedly greater SNS response to such traumamimetic (or threatening) stimuli, manifested by increased cardiovascular (e.g., systolic–diastolic, heart rate), skin conductance, and electromyographic (EMG) responses.

Increased Startle Response

The excessive startle response (or "jumpiness") observed in patients with PTSD was first reported by Kardiner (1941) in his landmark book on World War I veterans. Laboratory research has confirmed Kardiner's clinical observations by using a protocol that examines the physiological response evoked by loud and unexpected acoustic stimuli. The most common measure has been the eyeblink response to such bursts of sound, although cardiovascular indices have also been monitored. In general, the startle response among individuals with PTSD has been significantly greater than that among exposed individuals without the disorder (Pitman, Orr, Shalev, Metzger, & Mellman, 1999; Shalev, Orr, Peri, Schreiber, & Pitman, 1992).

Disrupted Sleep

Insomnia and traumatic nightmares have long been recognized as hallmarks of PTSD. Polysomnographic studies consistently show increased awakenings, reduced sleep time, and increased motor activity during sleep among those with PTSD. Some studies also suggest disrupted rapid eye movement (REM) sleep continuity, but this latter finding remains controversial (Mellman, Kulick-Bell, Ashlock, & Nolan, 1995; Pitman et al., 1999).

Traumatic nightmares appear to be unique events that differ significantly from Stage IV Night Terrors and REM Dream Anxiety Attacks (Friedman, 1981; Ross, Ball, Sullivan, & Caroff, 1989).

Tonic Physiological Arousal

The aforementioned observations, especially those concerning SNS hyperreactivity and the increased startle response, are clear indications of *phasic* abnormalities following exposure to discrete stimuli among individuals with PTSD. It appears that individuals with PTSD also exhibit excessive physiological manifestations at rest, or *tonic* abnormalities. A recent meta-analytic examination of basal cardiovascular activity indicated that individuals with PTSD have a higher resting heart rate and blood pressure in comparison with both trauma-exposed and nonexposed controls (Buckley & Kaloupek, 2001).

Adrenergic Abnormalities in PTSD

Given the physiological alterations mentioned previously and the crucial role of adrenergic mechanisms in the human stress response (Cannon, 1932), one might expect that PTSD would be associated with both tonic and phasic alterations of catecholaminergic function.

Tonic Adrenergic Activity

Evidence suggesting altered baseline catecholamine activity in PTSD is based on studies with 24-hour urinary levels and investigations of platelet and lymphocyte adrenergic receptors. Twenty-four hour urinary norepinephrine and epinephrine have been measured in male combat veterans, male and female Holocaust survivors, and female sexual abuse victims. Results have generally shown elevated catecholamine levels among individuals with PTSD compared with both trauma exposed–no-PTSD and nonexposed controls (see Southwick et al., 1999 for references).

It would be expected that increased catecholamine levels would produce a compensatory reduction (or down-regulation) of adrenergic receptors. This has been shown in research on both alpha-2 and beta adrenergic receptors. Two studies (with combat veterans and traumatized children, respectively) have shown reduced platelet alpha-2 binding sites among individuals with PTSD compared with controls (Perry, 1994; Perry, Giller, & Southwick, 1987). In addition, there is evidence that beta receptors are also down-regulated (Lerer, Gur, Bleich, & Newman, 1994).

Phasic Adrenergic Activity

As with the physiological findings, a variety of challenge studies have consistently demonstrated excessive phasic adrenergic responses among

individuals with PTSD. In addition to physiological hyperreactivity, exposure to psychological stressors has been associated with abrupt elevations in plasma epinephrine and norepinephrine, respectively, in two studies with combat veterans with PTSD (Blanchard et al., 1991; McFall, Murburg, Ko, & Veith, 1990).

Yohimbine, an alpha-2 adrenergic receptor antagonist, has been an important pharmacological probe in studies on phasic adrenergic activity. Yohimbine enhances adrenergic activity by blocking the inhibitory presynaptic alpha-2 receptor, thereby enhancing presynaptic release of norepinephrine. An investigation with Vietnam combat veterans found that among the participants with PTSD, yohimbine elicited panic attacks, combat-related flashbacks, and elevated brain adrenergic metabolism in contrast to veterans without PTSD who did not exhibit such abnormalities (Bremner, Innis, et al., 1997; Southwick et al., 1993).

Thus, studies on both physiological and catecholamine function indicate that the major adrenergic abnormality in PTSD is a hyperreactive phasic response, although alterations in tonic activity have also been detected.

Neuropeptide Y

NPY is a neuropeptide found in adrenergic neurons in the brain or SNS that is released along with norepinephrine during intense activation of the adrenergic system by yohimbine or excessive exercise (Pernow, 1988; Rasmusson et al., 2000). It apparently enhances the efficiency of adrenergic transmission in the SNS (Colmers & Bleakman, 1994) and appears to have a profound anxiety-reducing effect (Kask, Rago, & Harro, 1996). Of particular relevance to our previous discussion of HPA function, anxiolytic doses of NPY also antagonize the anxiogenic and other actions of CRF, making NPY a potential major moderator of the intensity of the human stress response (Britton et al., 1997). NPY is, therefore, an important neuropeptide to consider in PTSD because it is released during intense phasic activation of the adrenergic system and because it is a potent antagonist of CRF.

Veterans with PTSD exhibited significantly lower baseline NPY levels as well as a blunted NPY response to yohimbine in comparison to non-PTSD controls (Rasmusson et al., 2000). This is consistent with animal studies showing reduced NPY inhibition of adrenergic function following chronic stress (Corder, Castagne, Rivet, Mormede, & Gaillard, 1992). Indeed, it is possible that hypoactive NPY function contributes both to adrenergic hyperreactivity and increased CRF activity in PTSD (Rasmusson & Friedman, 2002).

Endogenous Opioids

CRF also activates the opioid peptide beta endorphin, which reciprocally inhibits both the adrenergic and HPA components of the human stress response. The little research on opioid activity in PTSD suggests that there may be both tonic and phasic abnormalities. Abnormal baseline opioid function has been detected among individuals with PTSD although the specifics of such findings have varied from study to study. Elevated cerebrospinal fluid beta endorphin levels were observed in male combat veterans with PTSD (Baker et al., 1997). Studies on plasma beta endorphin show mixed results: higher levels among Croatian women with PTSD due to the trauma of war (Sabioncello et al., 2000); normal levels in male combat veterans (Baker et al., 1997); and lower levels in a different cohort of combat veterans with PTSD (Hoffman, Burges Watson, Wilson, & Montgomery, 1989). There is also evidence that exposure of people with PTSD to relevant trauma-related stimuli (e.g., Vietnam veterans with PTSD viewing combat scenes) produces an abrupt phasic elevation in circulating opioid levels (Pitman, van der Kolk, Orr, & Greenberg, 1990).

Hypothalamic–Pituitary–Thyroid Axis

The HPA system has an important impact on HPT function. CRF and cortisol suppress both secretion of thyroid stimulating hormone (TSH) from the pituitary and conversion of thyroxine (T4) to the more metabolically active triiodothyronine (T3). Studies with combat veterans have demonstrated elevations in both T3 and T4. Such increases were positively associated with PTSD severity (Mason et al., 1995; Wang & Mason, 1999). Furthermore, unpublished observations on women with PTSD related to childhood sexual abuse (CSA), show higher T3 in comparison with female CSA survivors without PTSD (Friedman et al., 2001). Such findings suggest that chronic PTSD differs from chronic stress syndrome where TSH and T3 levels are reduced.

Hypothalamic–Pituitary–Gonadal Axis

Increased HPA activity suppresses all aspects of HPG function including secretion of gonadotropin-releasing hormone from the hypothalamus, follicle stimulating and luteinizing hormones from the pituitary, and estradiol and testosterone from the reproductive organs. Conflicting findings have been reported in two studies in which testosterone was measured in people with PTSD. Elevated serum (Mason et al., 1990), in contrast to reduced

cerebrospinal fluid (Mulchahey et al., 2001), testosterone levels were detected among male combat veterans with PTSD.

Growth Axis

Increased HPA activity interferes with growth axis function through inhibition of growth hormone release as well as through suppression of growth at target tissues. Vietnam combat veterans with and without PTSD showed no difference in growth hormone levels (Laudenslager et al., 1998). Another study, in which PTSD was not measured, may be relevant here. Sexually and physically abused boys (not assessed for PTSD) exhibited a blunted growth hormone response to both clonidine and levodopa, in contrast to nonabused control participants.

Metabolic Axis

Metabolic syndrome X (defined earlier) is a complex cluster of symptoms resulting from suppression of growth hormone, sex steroids, and bone production. The only research on this syndrome among individuals with PTSD has focused on osteopenia, a reflection of bone metabolism, which is an osteoporotic condition marked by a significant reduction in bone density. Among 140 male American naval aviators previously held as prisoners of war, those with PTSD exhibited greater frequency of osteopenia than those without PTSD, who were more likely to show normal bone density (Sausen, Moore, Ambrose, Wells, & Mitchell, 2001).

The Immune System

Because blood levels of lymphocyte or NK cells vary according to the dynamics of catecholamine and glucocorticoid secretion, we limit this brief review to functional measures of immunological activity such as NK cytotoxicity per cell, assays of cell proliferation, and the cytokine response to specific antigens (Dhabhar & McEwen, 1997). More comprehensive reviews can be found elsewhere (see Dougall & Baum, chap. 6, this volume; Schnurr & Jankowski, 1999). The results in people with chronic PTSD are mixed. Extrapolating from findings associated with chronic stress syndrome (shown in Table 7.1) one would expect to observe immunosuppression in individuals with chronic PTSD. Surprisingly, enhanced immunological function has actually been found more often than immunosuppression. Three studies on veterans with chronic PTSD observed higher cutaneous, cell-mediated immunity and higher cytokine levels among those with PTSD compared with a non-PTSD group (Burges Watson, Muller, Jones, & Bradley, 1993; Laudenslager et al., 1998; Spivak et al., 1997). In a fourth report, however,

immunological activation by antigens was no different among veterans with PTSD than among controls (Boscarino & Chang, 1999). Finally, Boscarino (1997) found that male Vietnam combat veterans with PTSD appeared to have reduced immunological function because they reported higher prevalence of nonsexually transmitted infectious disease than non-PTSD veterans.

Given the complexity of the immune system and given that both tonic and phasic abnormalities have been found in people with PTSD in most biological systems investigated, one way to reconcile these diverse findings is to postulate that there is both a tonic state of immunosuppression as well as an episodic or phasic state characterized by enhanced immunological function.

Comparison of Biological Abnormalities Associated With Chronic Stress Syndrome and PTSD

As with chronic stress syndrome, PTSD appears to be associated with significant alterations in function of the same key biological systems. Current evidence (shown in Table 7.1) suggests that specific abnormalities detected in these two pathological states may be quite similar in some respects and quite different in others. Data on physiological and LC/NE mechanisms seem most comparable whereas the pattern of HPA dysregulation may be most different. Research with opioids, HPT, HPG, growth and immunological systems is much too preliminary to invite serious speculation. Of greater importance is that allostatic load caused by the pathophysiology of both PTSD and chronic stress syndrome appears to increase the risk for medical illness. We explore the clinical consequences of these two pathological states in the following section.

HOW MIGHT PTSD-RELATED BIOLOGICAL ABNORMALITIES INCREASE THE RISK FOR MEDICAL ILLNESS?

Chronic stress syndrome is best understood as a cascade of reactions stimulated by CRF-induced actions on HPA, LC/NE, opioid, and immunological systems. Medical illnesses associated with this syndrome are well understood within such a conceptual framework (Chrousos, 1998; McEwen, 1998). As noted previously, the pathophysiology is less clear with respect to PTSD. Here, elevated CRF appears to produce a different pattern of HPA dysregulation marked by variable cortisol levels and alterations in glucocorticoid receptor sensitivity. For purposes of the present discussion, we propose that PTSD-related HPA dysregulation will generate clinically significant allostatic load that will increase the risk for medical illness. Tonic abnormalities, which will usually (but not always) promote increased HPA

activity (through higher CRF activity and possibly through enhanced glucocorticoid receptor sensitivity), are more likely to produce pathological changes similar to those associated with chronic stress syndrome. We further propose that phasic abnormalities are much more significant in PTSD and, therefore, more likely to produce the clinically significant allostatic load that distinguishes medical illnesses due to PTSD from those associated with chronic stress syndrome.

Physiological Abnormalities

We focus this discussion primarily on adrenergic abnormalities, reviewed previously, because the most prominent physiological alterations in PTSD involve SNS activity (which is adrenergic). With respect to both SNS and adrenergic function in PTSD, dramatic hyperreactivity has been observed much more consistently than tonic abnormalities.

Schneiderman (1977) first proposed that the abrupt increase in blood pressure and heart rate caused by stress-induced recurrent activation of the SNS produces hemodynamic disturbances that might produce atherosclerosis. He later proposed that heightened cardiovascular reactivity in response to psychological stressors might increase the risk for chronic heart disease (CHD) (Schneiderman, 1987). Other investigators have confirmed this prediction, showing that cardiovascular reactivity predicts the development of atherosclerosis (Everson et al., 1997). In addition, Shapiro (1988) found that cardiovascular reactivity to laboratory stressors predicts hypertension among (susceptible) individuals with a family history of this illness.

These findings concerning the risk for cardiovascular illness associated with chronic stress syndrome also apply to PTSD. Indeed, the risk may be even higher in PTSD, in which physiological and adrenergic hyperreactivity is such a prominent feature.

There are currently a few studies showing a positive relationship between PTSD and cardiovascular abnormalities (also see Green & Kimerling, chap. 2, this volume). Such findings include higher rates of angina (Falger et al., 1992), lower cardiovascular effort tolerance on a laboratory treadmill test (Shalev, Bleich, & Ursano, 1990), earlier onset of arterial disorders (Schnurr, Spiro, & Paris, 2000), and electrocardiogram abnormalities showing arterioventricular conduction defects and a myocardial infarction pattern (Boscarino & Chang, 1999).

Pain Syndromes

Abnormalities in opioid function would be expected to be expressed clinically as altered pain perception. Indeed, lower pain thresholds have been

observed among individuals with PTSD in comparison with nonaffected individuals (Perry, Cella, Falkenberg, Heidrich, & Goodwin, 1987; Shalev, Peri, Canetti, & Schreiber, 1996) and there are clinical reports of an association between chronic pain and PTSD (Benedikt & Kolb, 1986; Rapaport, 1987). Other pertinent literature has shown an association between trauma exposure and self-reported painful clinical complaints (see Friedman & Schnurr, 1995; Green & Kimerling, chap. 2, this volume), but such findings are only suggestive because PTSD was not diagnosed in most of these studies.

Endocrine, Metabolic, and Immunological Abnormalities

Clinical studies on the impact of PTSD on endocrine function are in their infancy. Laboratory studies, reviewed previously, have shown that individuals with PTSD have higher T3 compared with normal controls, although T3 levels for both groups were generally within the normal range. Although there are no data on thyroid abnormalities in PTSD, an interesting clinical report that is consistent with such laboratory findings, describes a marked increase in the number of documented cases ($n = 87$) of hyperthyroidism diagnosed in the same region of Bosnia during a 12-month period of war in contrast to the incidence of hyperthyroidism during the previous 12-month period of peacetime ($n = 54$). Without exception, wartime cases exhibited elevations in both T3 and T4 (Zubovic, Mikac, Biukovic, Skrobic, & Rajkovaca, 1993).

Because of the reciprocal relationship between HPA and HPG axes, one would predict that reproductive abnormalities would be more likely to occur among people with PTSD than among nonaffected individuals. This prediction was confirmed in the only published study on this question. After controlling for demographic and psychological factors, Seng and colleagues (2001) found that 455 women with PTSD had significantly higher odds of ectopic pregnancy, spontaneous abortion, preterm contractions, and excessive fetal growth, relative to 638 nonpsychiatric controls. This is consistent with other studies in which PTSD was not assessed, which have shown that women who experienced stressful life events around the time of conception or early gestation were more likely to deliver infants with certain congenital abnormalities (Carmichael & Shaw, 2000) and that domestic battering was associated with higher incidence of gynecological disorders and abortions that were not the direct result of injuries sustained during the physical abuse (Bergman & Brismar, 1991).

To date, there have not been any published clinical findings concerning the relationship between PTSD and the growth hormone axis. We predict that future research will show that normal growth and maturation can be

adversely affected by exposure to traumatic stress, especially if such exposure occurs during critical developmental periods of childhood and adolescence.

We previously reviewed the cluster of medical problems, called metabolic syndrome X, associated with chronic stress syndrome. It consists of a cluster of symptoms resulting from excessive HPA-induced suppression of growth hormone, gonadal steroids, and bone growth (see Table 7.2). We also cited the one relevant study, in this regard, showing abnormalities in bone metabolism (e.g., osteopenia) associated with PTSD among U.S. Navy repatriated prisoners of war (Sausen et al., 2001). Consistent with our argument that tonic HPA abnormalities in PTSD will generally resemble those seen with chronic stress syndrome, we would predict that people with PTSD are more likely than non-PTSD individuals to develop other manifestations of metabolic syndrome X in addition to osteopenia.

There is evidence for both suppression and enhancement of immunological function among people with PTSD. Given the complex web of interactions among HPA, adrenergic, and immunologic systems, phasic enhancement of immune activity could be triggered by CRF, norepinephrine, or by cytokines such as IL-6 (Crofford et al., 1997) or any combination of the above (Ader, Cohen, & Felten, 1995; Leonard & Song, 1996; Zakowski, McAllister, Deal, & Baum, 1992; Ziegler, Ruiz-Ramon, & Shapiro, 1993).

Such findings are consistent with a chronic pattern of tonic immunosuppression, punctuated by stress-induced phasic episodes of acute enhancement of immunological activity. In the case of moderate-to-severe PTSD, it is possible that phasic episodes are of sufficient frequency and intensity to obscure the underlying tonic immunosuppression, thereby presenting a cross-sectional picture of enhanced immunological activity as has been found in several studies cited previously. One possible mechanism could be stress-enhanced inflammatory cytokine production superimposed on a tonic state of relative glucocorticoid deficiency. This is consistent with the phenomenology of a number of clinical states marked by episodic stress-induced increased incidence or exacerbation of symptoms. The list of medical conditions exacerbated by acute stress includes rheumatoid arthritis (Potter & Zautra, 1997), Type I diabetes (American Diabetes Association, 1997; Ionescu-Tirgoviste, Simion, Mariana, Dan, & Iulian, 1987), fibromyalgia and chronic fatigue syndrome (Crofford & Demitrack, 1996; Crofford, Jacobson, & Young, 1999), irritable bowel syndrome (Anton & Shanahan, 1998), temporomandibular disorders (Korszun, Papadopoulos, Demitrack, Engleberg, & Crofford, 1998), tension headaches, dysmenorrhea, irritable bladder syndrome (see Crofford et al., 1999), and multiple chemical sensitivity (Rowat, 1998).

Comparison of Medical Problems Associated With Chronic Stress Syndrome and PTSD

Both chronic stress syndrome and PTSD appear to be associated with a number of medical illnesses. Although PTSD research on this question is at an early stage, current evidence (shown in Table 7.2) indicates a remarkable consistency in the medical consequences of these two pathological states. This is most apparent in studies concerning cardiovascular abnormalities. The few clinical abnormalities related to opioid, thyroid, reproductive, metabolic, and immunological function also suggest how PTSD could lead to medical problems.

HOW DOES THE ALLOSTATIC LOAD MODEL ENHANCE OUR UNDERSTANDING OF THE ETIOLOGICAL SIGNIFICANCE OF SUCH ABNORMALITIES?

Although many specific PTSD-related biological abnormalities and associated disease entities are shown in Tables 7.1 and 7.2, they are all consequences of tonic and phasic alterations in the human mediators of the stress response. More generally, using the terminology of allostasis, which broadens the discussion beyond "stress" per se, these PTSD abnormalities reflect an imbalance in various systems that usually help the body to adapt to a variety of challenges, be they related to lifestyle (diet, exercise, smoking, alcohol) or to stressful life events. Dysregulation of HPA, adrenergic, metabolic, and immune mechanisms produces secondary abnormalities through a cascade of downstream mechanisms that all play crucial roles in the maintenance of homeostasis and health. This is the essence of the organizing concepts of allostatic states and allostatic load.

The psychobiological demands of chronic PTSD result in allostatic states of sustained activity that enable the organism to achieve a new steady state through which to maintain vital functions. "The price of this accommodation to stress can be *allostatic load*, which is the wear and tear that results from chronic overactivity or underactivity of allostatic systems" (McEwen, 1998). This allostatic state promotes pathophysiological changes over time. It is these changes that increase vulnerability to medical illness among individuals with PTSD.

McEwen (1998) has identified four types of allostatic states that result in allostatic load and, in turn, increase the risk for medical illness. We review each one and show that all four types of allostatic load are present in PTSD. Type 1 allostatic load (Figure 7.1) is "repeated 'hits' from multiple stressors," such as repeated surges of blood pressure that can trigger

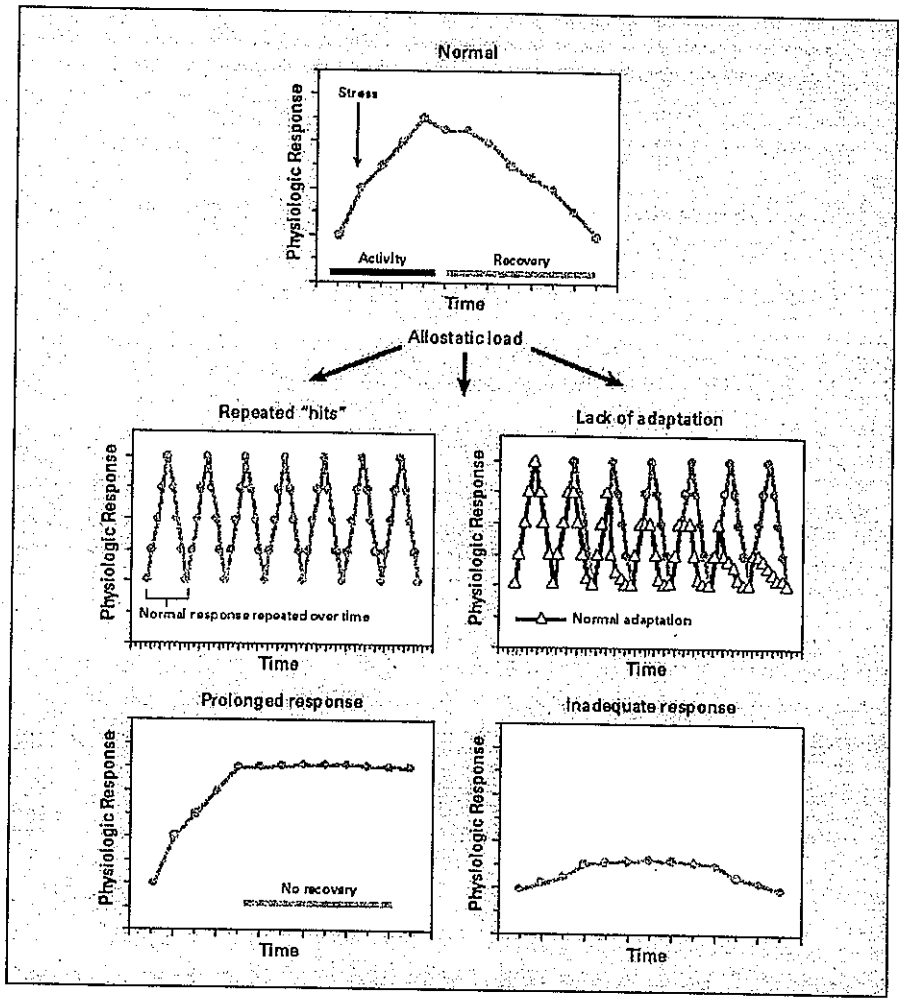

Figure 7.1. Four types of allostatic load. The top panel illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load; repeated "hits" from multiple stressors; lack of adaptation; prolonged response due to delayed shutdown; and inadequate response that leads to compensatory hyperactivity of other mediators (e.g., inadequate secretion of glucocorticoids, resulting in increased concentrations of cytokines that are normally counterregulated by glucocorticoids). From "Protective and Damaging Effects of Stress Mediators," by B. S. McEwen, 1998, *New England Journal of Medicine, 338,* p. 174. Copyright 1998 by the Massachusetts Medical Society. Reprinted with permission.

myocardial infarction or atherosclerosis in susceptible individuals (Muller, Tofler, & Stone, 1989). As discussed previously, a number of phasic abnormalities in PTSD appear to exemplify this type of allostatic load. Most notably, they include cardiovascular and adrenergic hyperreactivity to environmental demands that are experienced as stressful. In addition, traumatic reminders, intrusive recollections, and traumamimetic stimuli can all elicit cardiovascular hyperreactivity among individuals with PTSD. Other hyperreactive mechanisms in PTSD appear to include glucocorticoid receptor supersensitivity and enhanced immune response to acutely stressful situations. As shown in Table 7.2, these may contribute to exacerbation of chronic disease states, allergic conditions, and autoimmune diseases.

Allostasis is not only an outgrowth of past experiences but may be based in part on the expectation of future events. Although realistic anticipation is certainly adaptive, problems may arise if expectations are not well calibrated to external reality. Thus, abnormalities may occur in the accuracy of stress and threat appraisal rather than with responsivity to reality per se. Problems in signal detection may take one of two possible forms; either the individual fails to recognize important stressors to which he or she must respond (i.e., false negatives) or the individual misinterprets harmless stimuli as threats to survival (i.e., false positives). False positives are common in PTSD. Most often, affected individuals misperceive danger during conditions of safety. This general tendency to perceive false positive threat signals produces a response bias toward hyperreactivity. In other words, the threat-averse, hypervigilant person with PTSD is more likely to experience danger in nondangerous situations and, therefore, elicit stress responses unnecessarily. Pathophysiologic manifestations of hypervigilance may include glucocorticoid enhanced negative feedback responsivity, startle response hyperreactivity and possibly CRF activation, stress-induced analgesia, and cytokine mediated mobilization of the immune system. In short, Type 1 allostatic load is a common occurrence in PTSD.

Type 2 allostatic load (Figure 7.1), "lack of adaptation," results from a progressive allostatic state in which the organism loses its capacity to habituate or adapt to repeated stressors. Failure to habituate—that is, to dampen physiological responses to the same stressor over time—results in excessive and potentially deleterious overexposure to the various components of the stress response. An experimental example of Type 2 allostatic load in PTSD is seen in resistance to extinction of the acoustic startle response (Shalev et al., 1992). Type 2 allostatic load might also result from sensitization or kindling of limbic nuclei as proposed by Post and associates (Post, Weiss, Li, Leverich, & Pert, 1999; Post, Weiss, & Smith, 1995) in which repeated exposure to stressful or traumatic stimuli produces a progressive enhancement (rather than habituation) of the stress response among affected individuals. It may also be relevant to episodic flare-ups of chronic

illness under stressful circumstances (e.g., irritable bowel syndrome, rheumatoid arthritis).

Allostatic load Type 3, "prolonged response," is the result of an allostatic state reflecting the failure to shut off the allostatic response when it is no longer needed. Prolonged phasic elevations in cardiovascular, HPA, and immunologic activity are all applicable here and would very likely increase the risk for pathological states in those systems.

Whereas allostatic load Type 2 is a pathological phasic response, allostatic load Type 3 is primarily a tonic abnormality. This includes tonic elevations of blood pressure and heart rate that constitute a risk for cardiovascular disease. Prolonged HPA hyperactivity promotes immunosuppression, with all the previously described potential complications of such a state, including reduced disease resistance, cancer susceptibility and autoimmune problems. Chronically elevated HPA activity will also produce endocrine (thyroid, gonadotropic, and growth hormone), metabolic, and opioid system dysregulation as previously described.

Allostatic load Type 4, "inadequate response," is a more chronic state in which key components of the stress system have lost their capacity to mount an adequate response. This can result from depleted resources, irreversible consequences of prolonged suppression, or other mechanisms. An example offered elsewhere might also apply to PTSD: An inadequate HPA response is unable to terminate the mobilization of lymphocytes and NK cells during an acute inflammatory episode (McEwen, 1998). Under such conditions, the apparent clinical problem of excessive immunologic activity is really caused by an insufficient HPA response, which normally contains the immune response. Another example of allostatic load Type 4 is hypocortisolism, which predisposes individuals to several stress-related medical disorders such as chronic fatigue syndrome, fibromyalgia, somatoform disorders, idiopathic pain syndromes, rheumatoid arthritis, and asthma. Whether any or all of these syndromes will prove to be associated with PTSD remains to be seen.

Psychological, behavioral, and social factors observed in PTSD that promote its association with medical illness (see Schnurr & Jankowski, 1999; Seeman & McEwen, 1996) can also be understood in terms of allostatic load. These factors constitute the lifestyle of individuals with PTSD, and they contribute to the physiological responses that constitute allostasis. Maladaptive behavioral responses to stressors, such as smoking and ethanol consumption, ingestion of high fat diets, and lack of exercise, all intensify allostatic states and exacerbate allostatic load (see McEwen, 1998; Schnurr & Jankowski, 1999). As noted by Schnurr and Jankowski (1999), the heuristic value of applying the allostatic load model to PTSD is "its multivariate, longitudinal perspective and an emphasis on the cumulative and interactive effects" (p. 301) of a large number of chronic, disease-enhancing elements

that produce clinically significant "wear and tear" on individuals with this disorder.

HOW MIGHT THE ALLOSTATIC LOAD MODEL HELP US APPROACH RESILIENCE, PREVENTION, AND TREATMENT?

Allostatic load provides a conceptually coherent and parsimonious model with which to understand how the many diverse abnormalities associated with PTSD increase the risk for medical illness. It places the pathophysiological focus on the stress response as a whole, rather than on a specific dysregulation in a psychobiological system. Whether it is a tonic or phasic abnormality, the wear and tear on the system maintaining vital functions comes at a price that increases vulnerability to a large variety of medical disorders.

Allostasis, stability through change, does not necessarily imply a change for the worse. Changing behavior to promote regular exercise, judicious diet, stress reduction, psychological wellness, loving relationships, social support, and a sense of control over one's life, all have a salutary impact on health (McEwen, 1998; Seeman & McEwen, 1996). Dienstbier's (1989) concept of physiological toughening through aerobic exercises and other salubrious activities is also relevant here. Such measures provide an extra margin of safety with which to buffer the potentially deleterious impact of traumatic stress. We refer to allostatic change in such positive directions as *allostatic support* to differentiate it from the pathophysiological changes denoted by allostatic load.

We define allostatic support as any nonhomeostatic, biopsychosocial strategy that will oppose allostatic load. Individuals endowed with a healthy titer of inherited or acquired allostatic support are resilient. Conscious individual or societal efforts to increase allostatic support are likely to foster prevention of adverse health consequences. Efforts to reduce allostatic load by enhancing allostatic support constitute treatment.

Resilience, prevention, and treatment of PTSD might result from enhancing allostatic support in any of the psychobiological systems discussed previously (see Friedman, 2002). Such approaches should be effective whether allostatic load (constitutionally) preceded the onset of PTSD or occurred after an individual acquired the disorder. We believe that two of the most promising lines of research would focus on reducing hyperreactivity and normalizing dysregulated HPA function. A third approach might focus on increasing anabolic factors, such as GH, IGF-1, testosterone, or neurotrophins in the brain, to promote allostatic support.

Allostatic load Type 2 (Figure 7.1) is hyperreactivity that is sustained because of a failure of habituation or resistance to extinction. Because most

people exposed to traumatic stress do not develop PTSD (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995) it may be inferred that most people are resilient because they are equipped with inherited or acquired allostatic support mechanisms that effectively buffer the intense stress response triggered by exposure to a traumatic event, or that allow it to habituate subsequently. Theoretically, a preventive strategy (especially desirable for people entering potentially traumatizing professions such as the military, police work, and so forth) might consist of confidential screening procedures by which to identify deficiencies in one or more allostatic support capacities. Individuals wishing to overcome such deficits might request special psychophysiological training or physiological toughening designed to mobilize and enhance their capacity for habituation and extinction of excessive stress reactions (Dienstbier, 1989; Shalev, 1999). We expect that this type of voluntary preventive approach could attenuate the potentially deleterious effects of hyperreactivity, by fostering resilience and preventing the subsequent development of PTSD.

A second example emphasizes efforts to reduce allostatic load, or promote allostatic support, with respect to HPA dysregulation. This might be achieved with pharmacological agents that reduce CRF activity, such as CRF antagonists. It might also be achieved with prophylactic administration of cortisol, as in a study on septic shock in which modest cortisol doses reduced the incidence of PTSD (Schelling et al., 1999).

A third approach might be with medications that enhance NPY's capacity to inhibit both CRF and catecholamine activity. An experiment with American special forces military personnel exposed to an extremely stressful training experience showed that individuals who were best able to mobilize NPY tolerated the experience better than those with lower NPY levels (Morgan et al., 2000). This suggests that the capacity to efficiently mobilize NPY may be a marker of resilience against PTSD. It also suggests that people in dangerous professions who lack such a capacity might benefit from pretraumatic NPY administration (prevention) or posttraumatic NPY treatment to forestall the later development of PTSD.

Other examples of allostatic support will undoubtedly become apparent as we learn more about the pathophysiology of PTSD. In coming years, we expect that new ways to promote allostatic support will emerge that will foster resilience, prevent PTSD, and provide effective treatment (Friedman, 2002).

CONCLUSIONS AND FUTURE DIRECTIONS

PTSD is a major public health problem. We have proposed in this chapter that in addition to psychiatric morbidity, the complex pathophysiology of PTSD makes it a risk factor for a wide spectrum of medical disorders.

Research has just begun to demonstrate that the medical morbidity of PTSD may be at least as significant as its deleterious psychiatric consequences. Furthermore, individuals with PTSD are more likely to seek treatment from primary and specialty medical practitioners than from mental health professionals. A major reason they seek such treatment is because PTSD-related dysregulation of HPA, LC/NE, opioid, endocrine, metabolic, and immune systems can produce clinically significant medical illness.

We hope that the theoretical context and specific information presented in this chapter will promote better recognition of the wide array of medical and psychiatric sequelae among individuals who have PTSD.

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